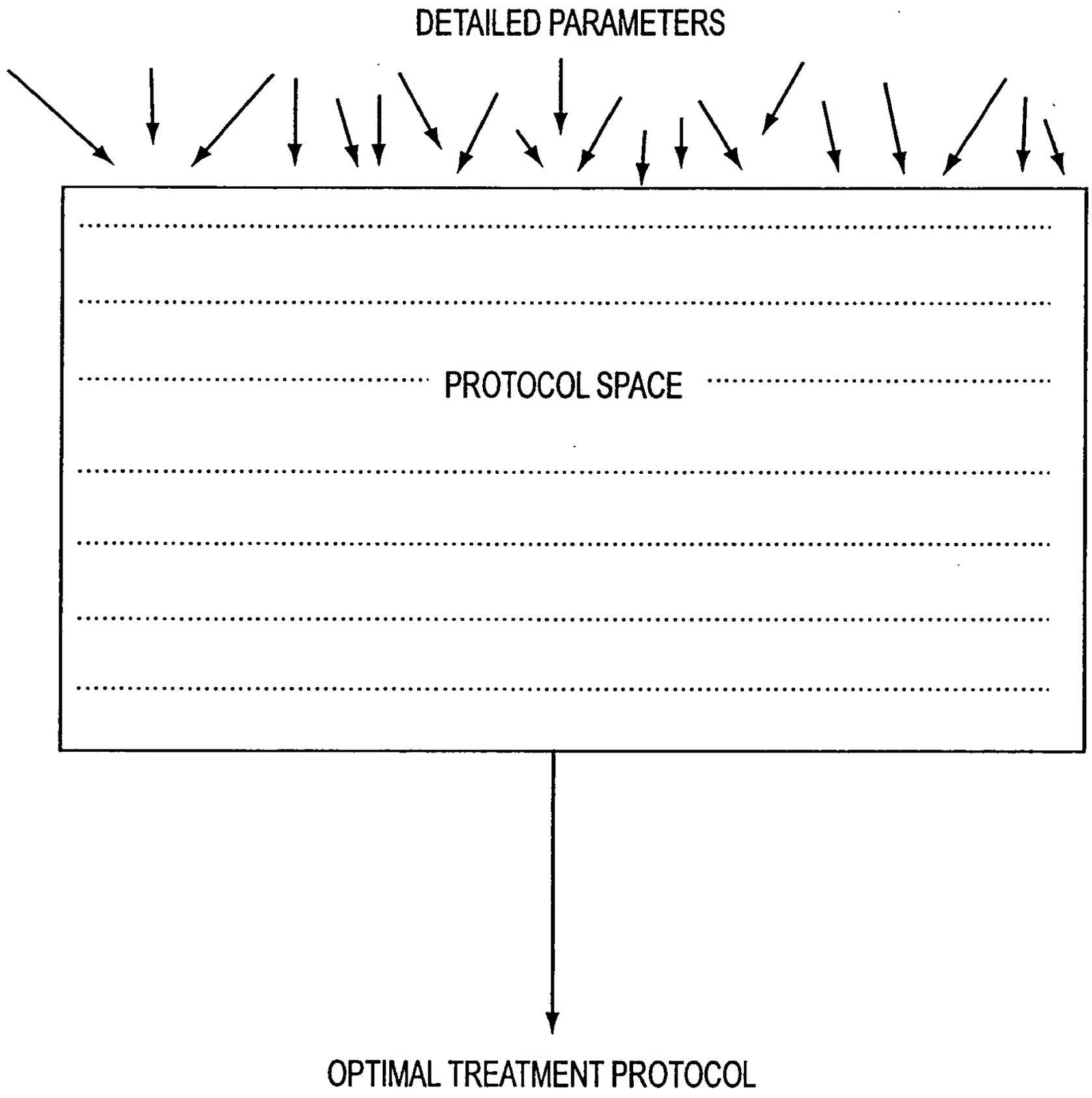

FIG. 1

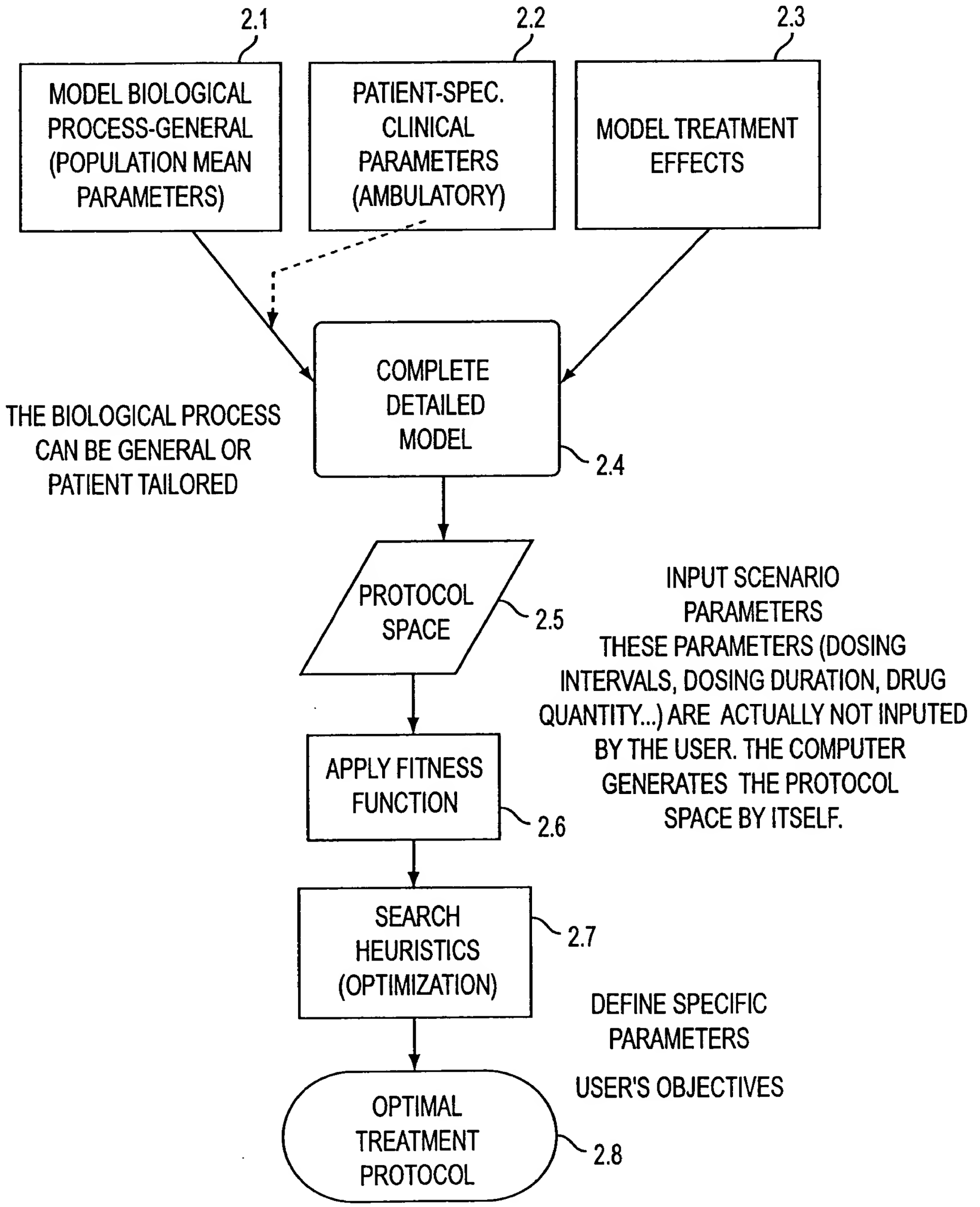
2.1
2.2
2.3
MODEL BIOLOGICAL PROCESS-GENERAL (POPULATION MEAN PARAMETERS)
PATIENT-SPEC. CLINICAL PARAMETERS (AMBULATORY)
MODEL TREATMENT EFFECTS
COMPLETE DETAILED MODEL
2.4
THE BIOLOGICAL PROCESS CAN BE GENERAL OR PATIENT TAILORED
PROTOCOL SPACE
2.5
INPUT SCENARIO PARAMETERS
THESE PARAMETERS (DOSING INTERVALS, DOSING DURATION, DRUG QUANTITY...) ARE ACTUALLY NOT INPUTED BY THE USER. THE COMPUTER GENERATES THE PROTOCOL SPACE BY ITSELF.
APPLY FITNESS FUNCTION
2.6
SEARCH HEURISTICS (OPTIMIZATION)
2.7
DEFINE SPECIFIC PARAMETERS
USER'S OBJECTIVES
OPTIMAL TREATMENT PROTOCOL
2.8

FIG. 2A

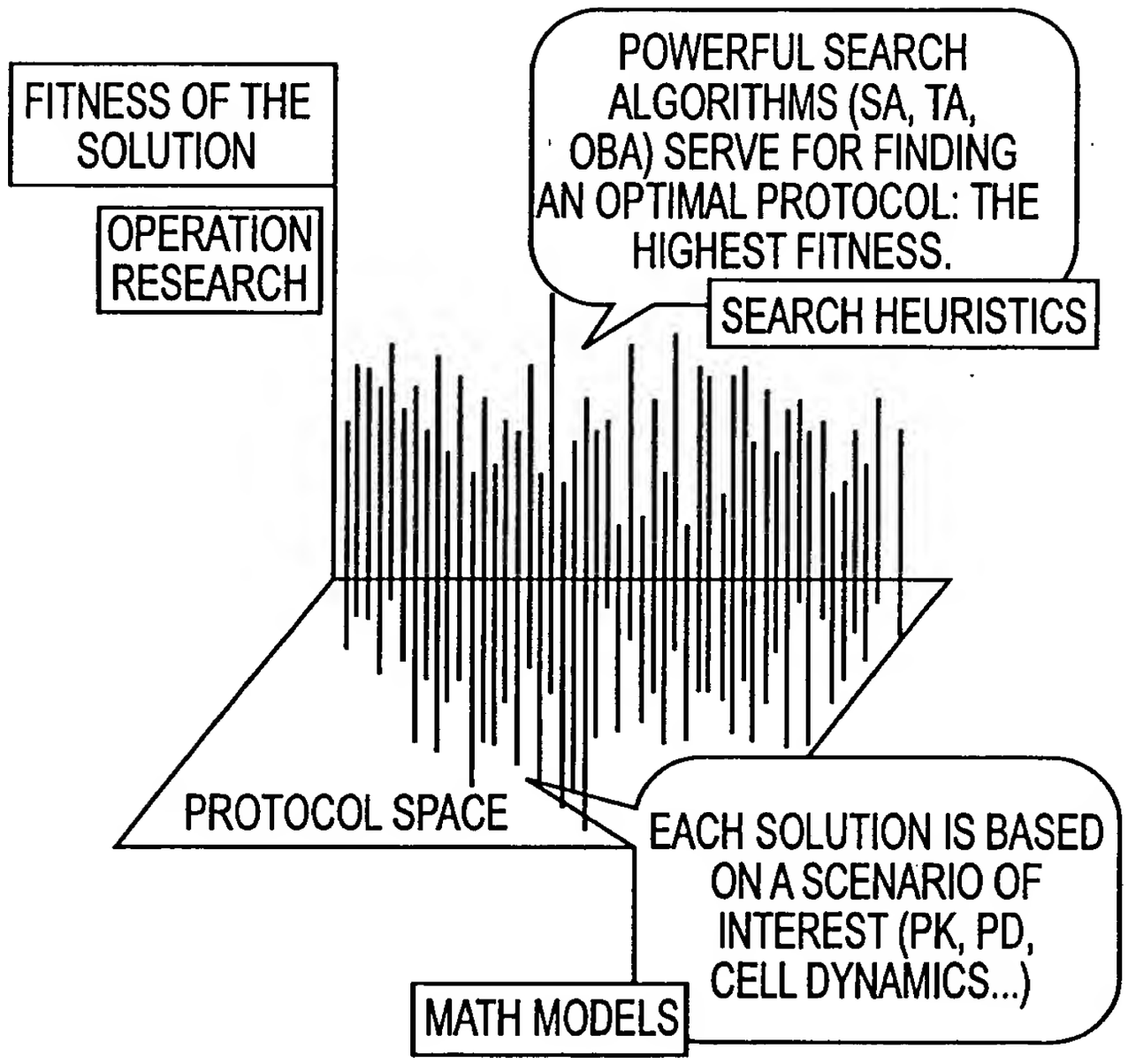
FITNESS OF THE SOLUTION
OPERATION RESEARCH
POWERFUL SEARCH ALGORITHMS (SA, TA, OBA) SERVE FOR FINDING AN OPTIMAL PROTOCOL: THE HIGHEST FITNESS.
SEARCH HEURISTICS
PROTOCOL SPACE
EACH SOLUTION IS BASED ON A SCENARIO OF INTEREST (PK, PD, CELL DYNAMICS...)
MATH MODELS

FIG. 2B

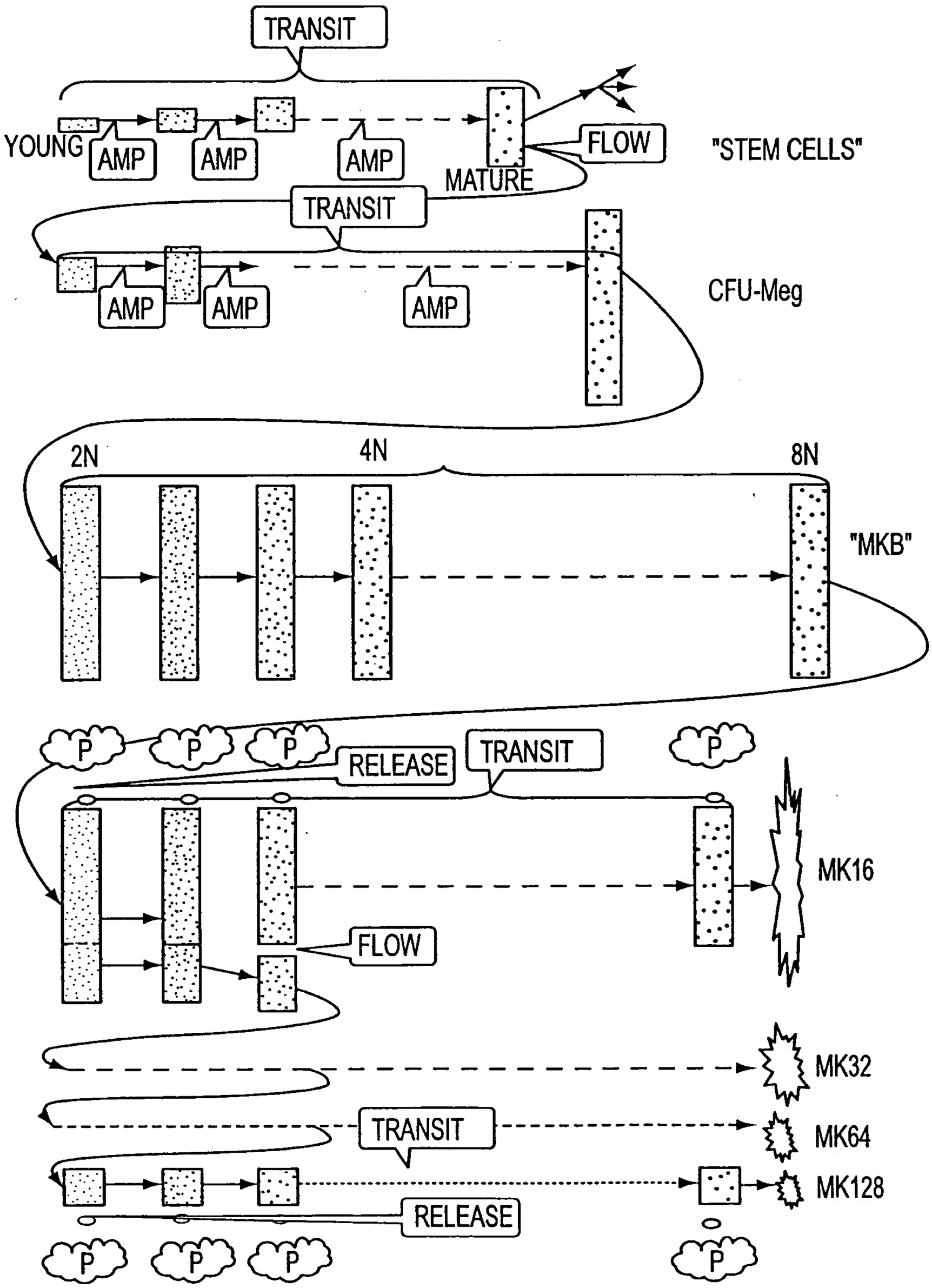
TRANSIT
YOUNG
AMP
AMP
AMP
MATURE
FLOW
"STEM CELLS"
TRANSIT
AMP
AMP
AMP
CFU-Meg
2N
4N
8N
"MKB"
P
P
P
RELEASE
TRANSIT
P
MK16
FLOW
MK32
TRANSIT
MK64
MK128
RELEASE
P
P
P
P

FIG. 3

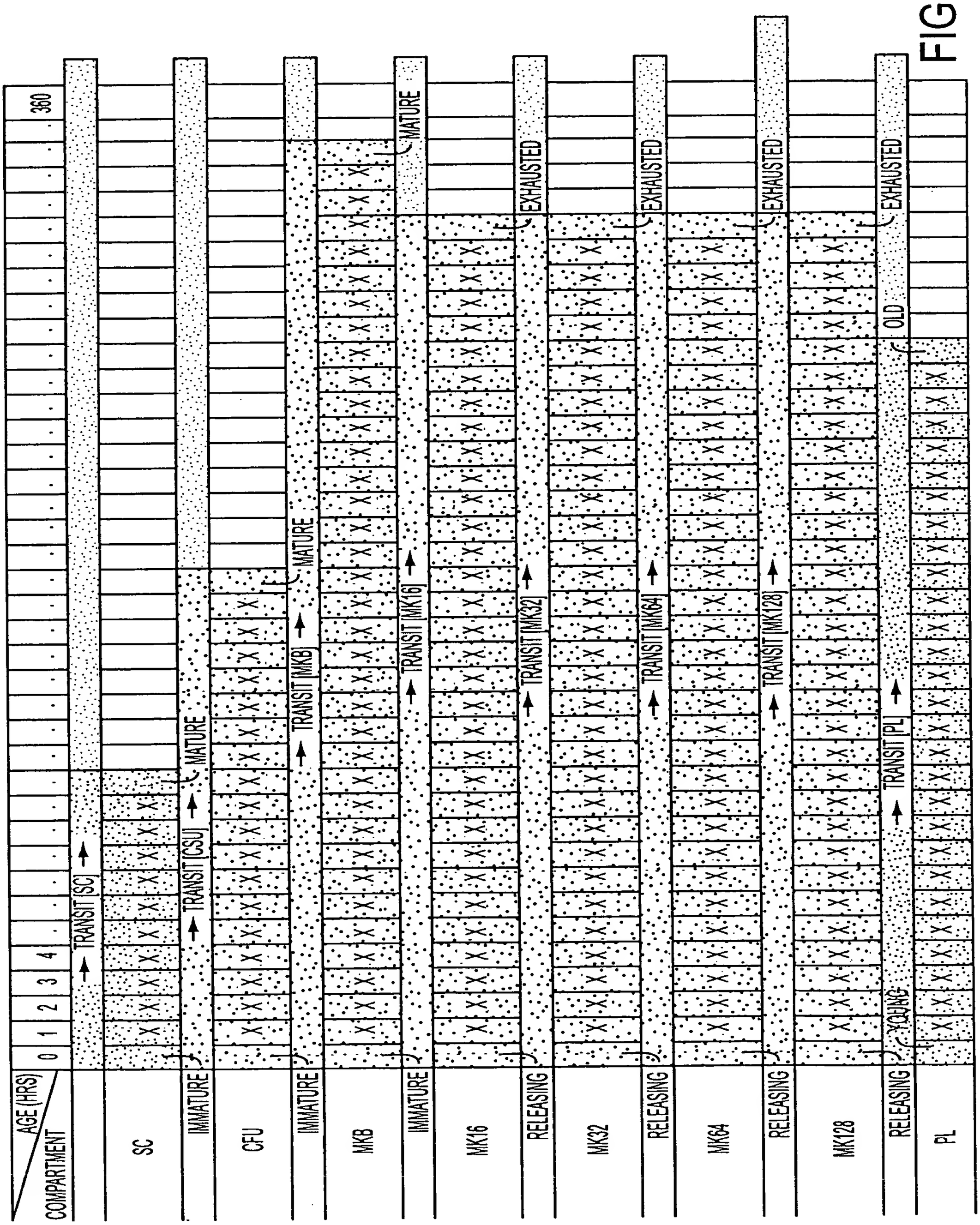
360
MATURE
EXHAUSTED
EXHAUSTED
EXHAUSTED
OLD
MATURE
TRANSIT [MKB]
TRANSIT [MK16]
TRANSIT [MK32]
TRANSIT [MK64]
TRANSIT [MK128]
TRANSIT [PL]
MATURE
TRANSIT [SC]
TRANSIT [CSU]
AGE (HRS)
COMPARTMENT
0
1
2
3
4
SC
IMMATURE
CFU
IMMATURE
MKB
IMMATURE
MK16
RELEASING
MK32
RELEASING
MK64
RELEASING
MK128
RELEASING
PL
XQUNG

FIG. 4

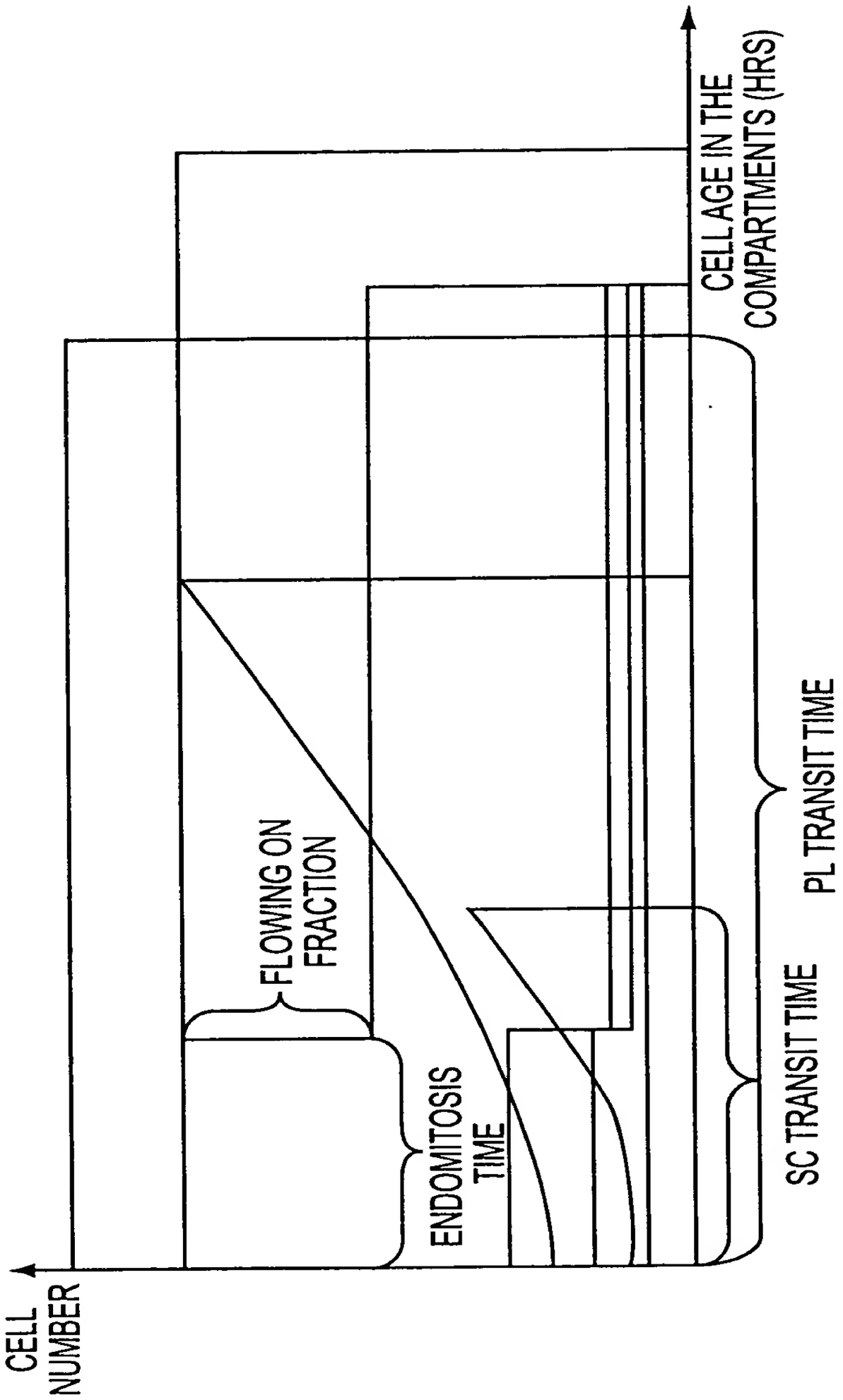
CELL NUMBER
CELLAGE IN THE COMPARTMENTS (HRS)
FLOWING ON FRACTION
ENDOMITOSIS TIME
SC TRANSIT TIME
PL TRANSIT TIME

FIG. 5

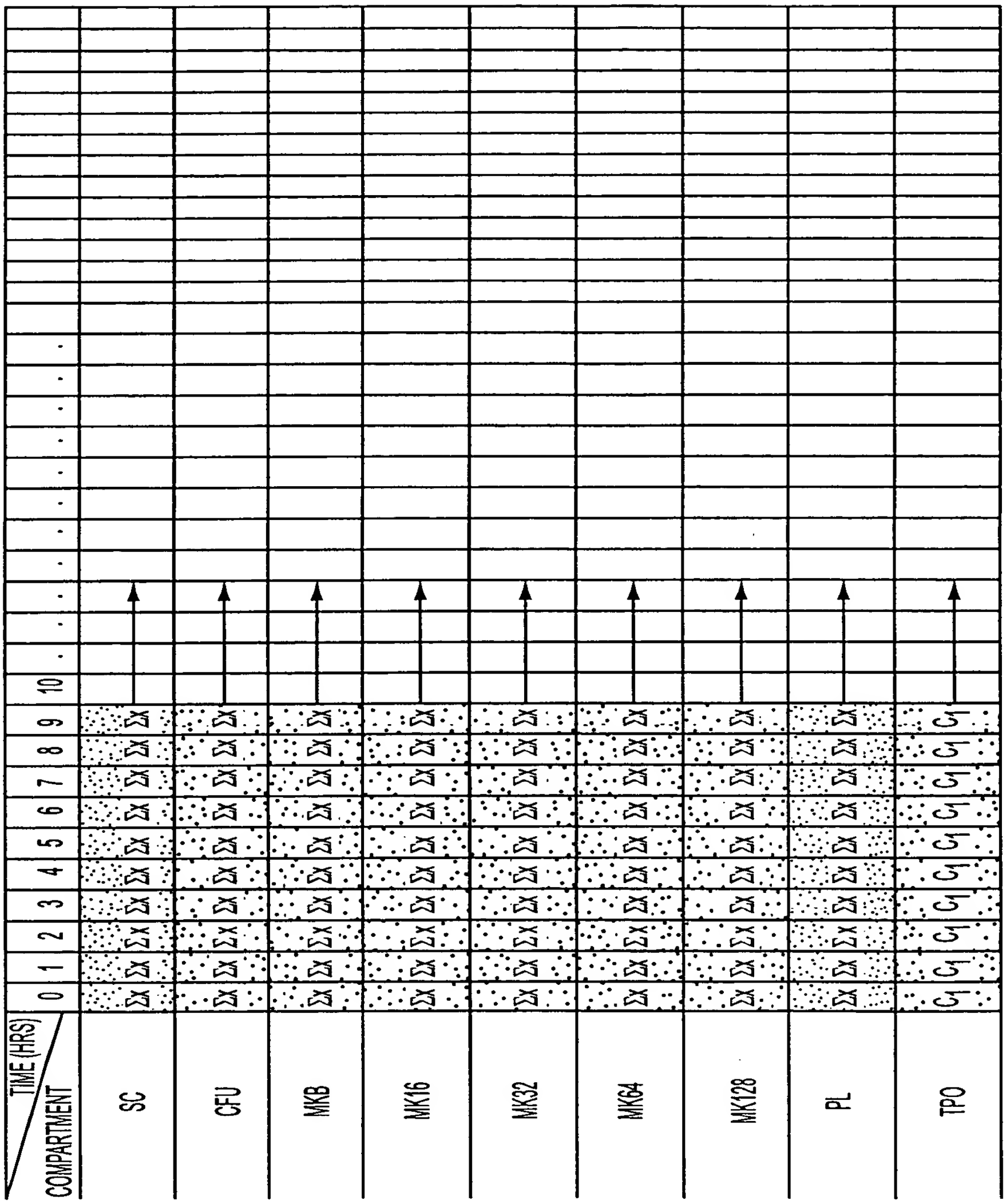
TIME (HRS)
COMPARTMENT
0
1
2
3
4
5
6
7
8
9
10
SC
CFU
MKB
MK16
MK32
MK64
MK128
PL
TPO
ΣX
C1

FIG. 6

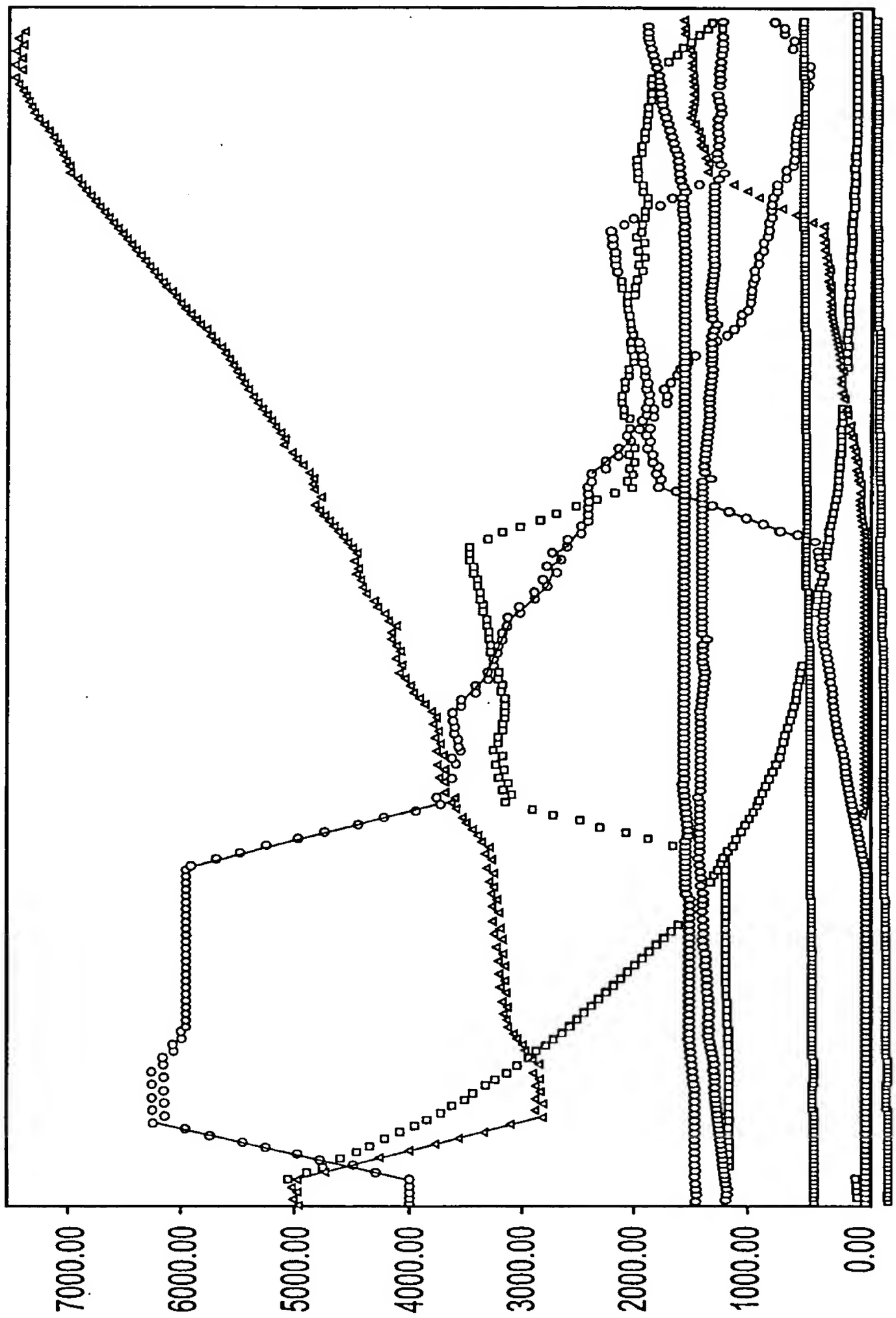

FIG. 7

SIMULATIONS SHOWING THAT IF THE PROTOCOL IS PRE-CALCULATED THEN A SIMILAR OR A HIGHER EFFICACY CAN BE OBTAINED USING 4-FOLD REDUCED TOTAL DOSE OF TPO.

TPO USE IN HEALTHY DONORS:

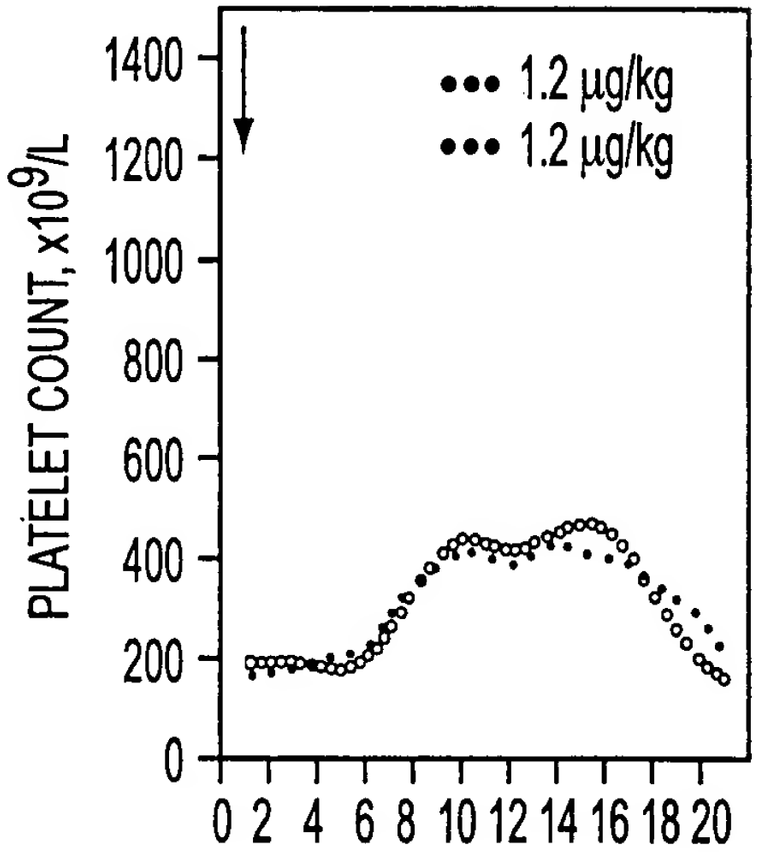

FIG. 8A

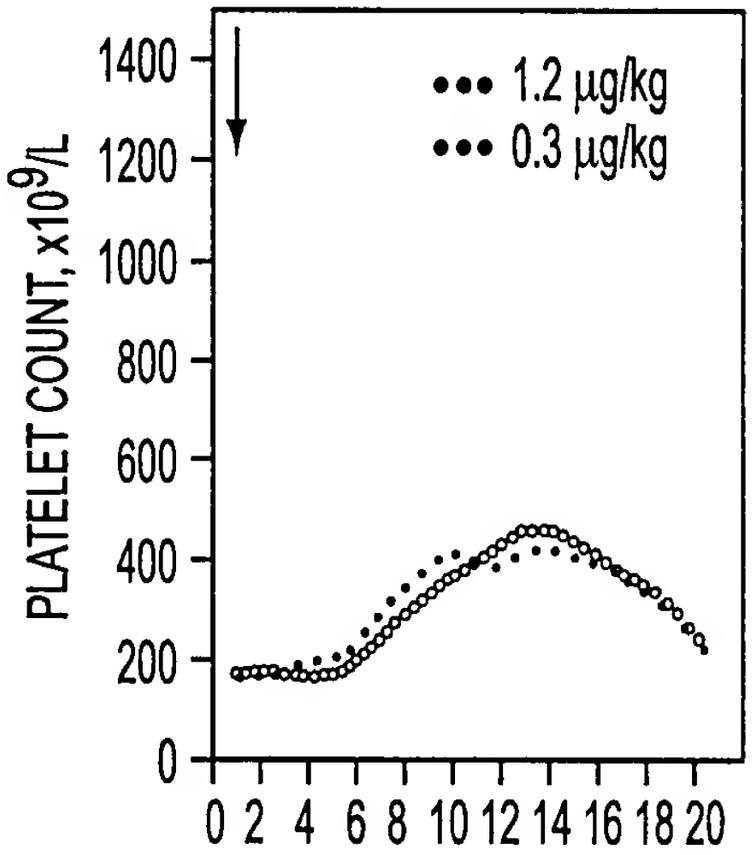

FIG. 8B

FIG. 8: TPO GIVEN TO HEALTHY DONORS- RESULTS OF TPO CLINICAL TRIALS FROM RECENT RESEARCH ON HEALTHY PLATELET DONORS, AS COMPARED TO OUR COMPUTER SIMULATION RESULTS. ARROWS INDICATE THE START OF TPO TREATMENT. (A) COMPARISON OF EXPERIMENTAL DATA FROM PUBLISHED ARTICLES[1] (BLACK) AND OUR MODEL SIMULATION (GREEN), IN BOTH TPO WAS GIVEN AS A SINGLE IV DOSE OF 1.2 µg/kg ON DAY 0. (B) COMPARISON OF THE SAME EXPERIMENTAL DATA (BLACK) AND OUR PROPOSED TPO ADMINISTRATION PROTOCOL; THE TOTAL DOSE IN THE SIMULATED PROTOCOL WAS 0.3 µg/kg (BLUE).

Appln. No. 09/691,053
Docket No. Q60688
In response to Notice of Allowability
dated September 9, 2004
Formal Drawings
9 of 16

SIMULATIONS SHOWING THAT IF THE PROTOCOL IS PRE-CALCULATED THEN A SIMILAR OR A HIGHER EFFICACY CAN BE OBTAINED USING 4-FOLD REDUCED TOTAL DOSE OF TPO.

TPO USE IN PATIENTS RECEIVING CHEMOTHERAPY:

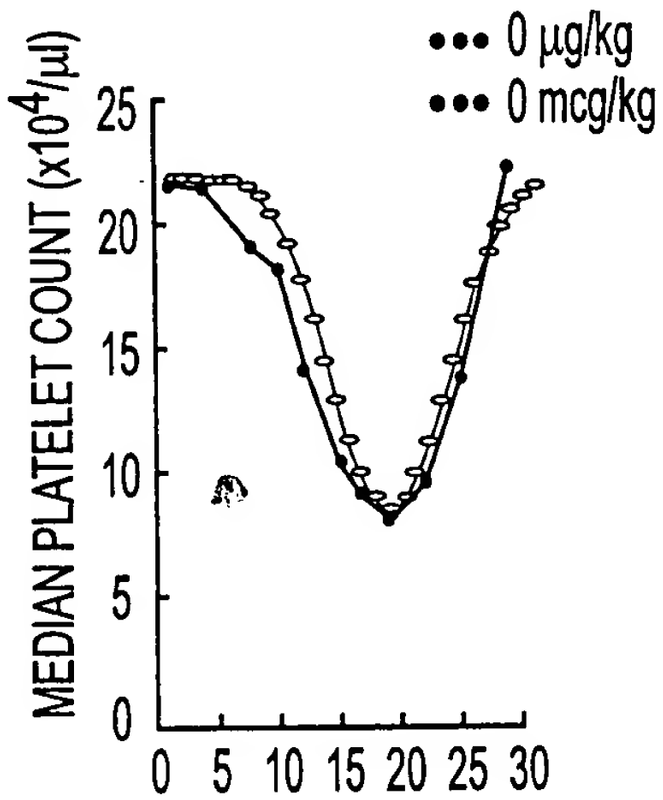

FIG. 9A

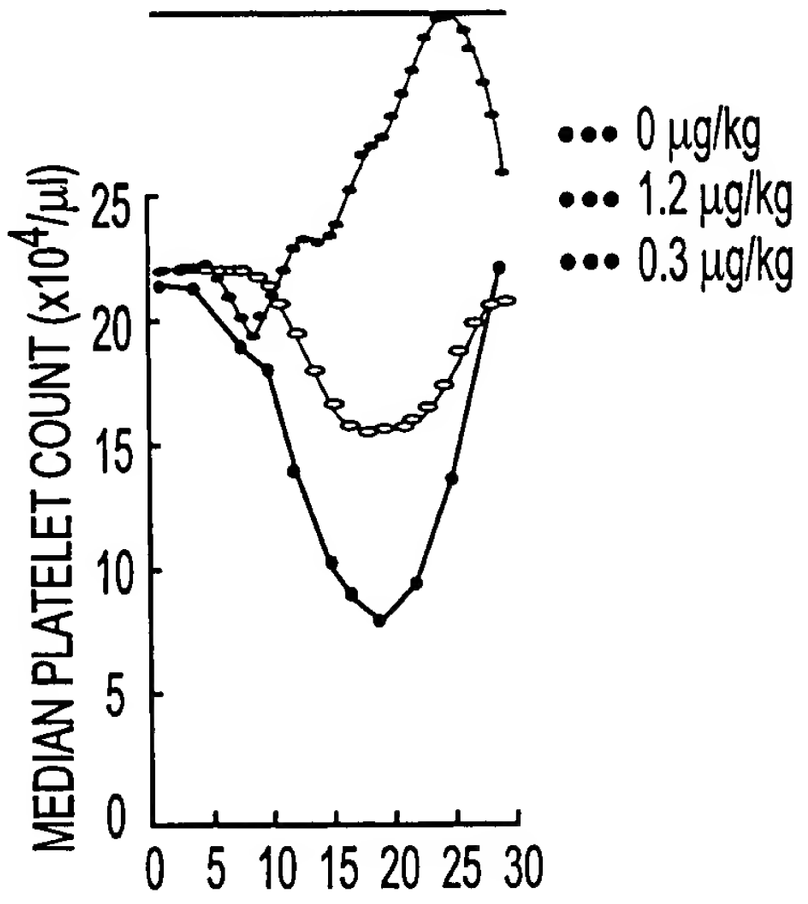

FIG. 9B

FIG. 9: TPO WITH CHEMOTHERAPY- (A) RESULTS OF CLINICAL TRIALS FROM RECENT RESEARCH ON THROMBOCYTOPENIA INDUCED IN PATIENTS RECEIVING SINGLE CARBOPLATIN CHEMOTHERAPY[2] ON DAY 0 (BLACK), AS COMPARED TO OUR MODEL SIMULATION OF THESE RESULTS (GREEN). (B) THE SAME EXPERIMENTAL DATA (BLACK); SIMULATIONS OF THE SAME EXPERIMENT, WITH ADDITION OF "CONVENTIONAL" TPO PROTOCOL OF A SINGLE IV DOSE OF 1.2 µg/kg ON DAY 0 (OLIVE); SIMULATIONS OF THE SAME EXPERIMENT UNDER OUR PROPOSED PROTOCOL THAT TOTALS 0.3 µg/kg (BLUE).

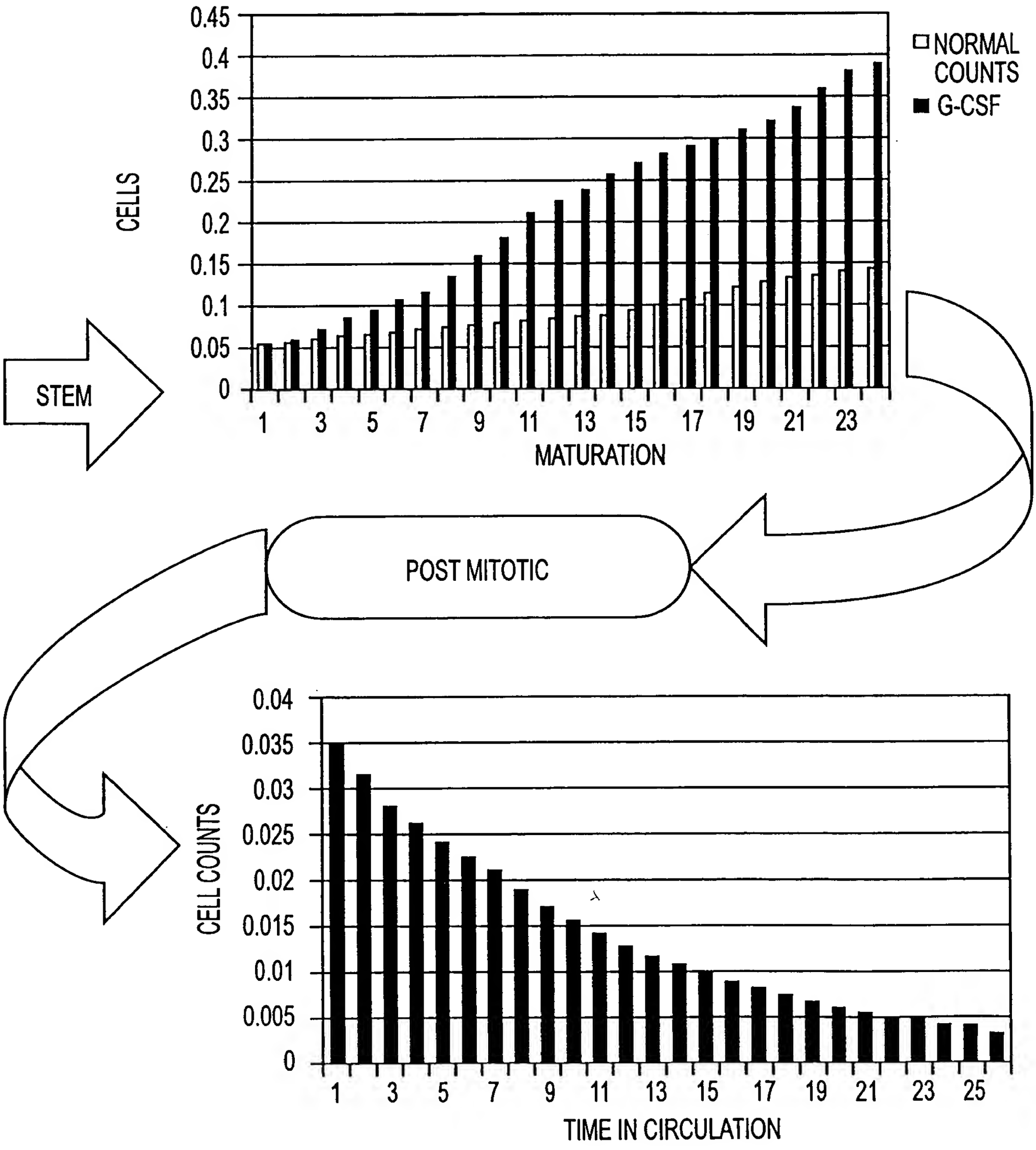
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
CELLS
NORMAL COUNTS
G-CSF
1 3 5 7 9 11 13 15 17 19 21 23
MATURATION
STEM
POST MITOTIC
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
CELL COUNTS
1 3 5 7 9 11 13 15 17 19 21 23 25
TIME IN CIRCULATION

FIG. 10

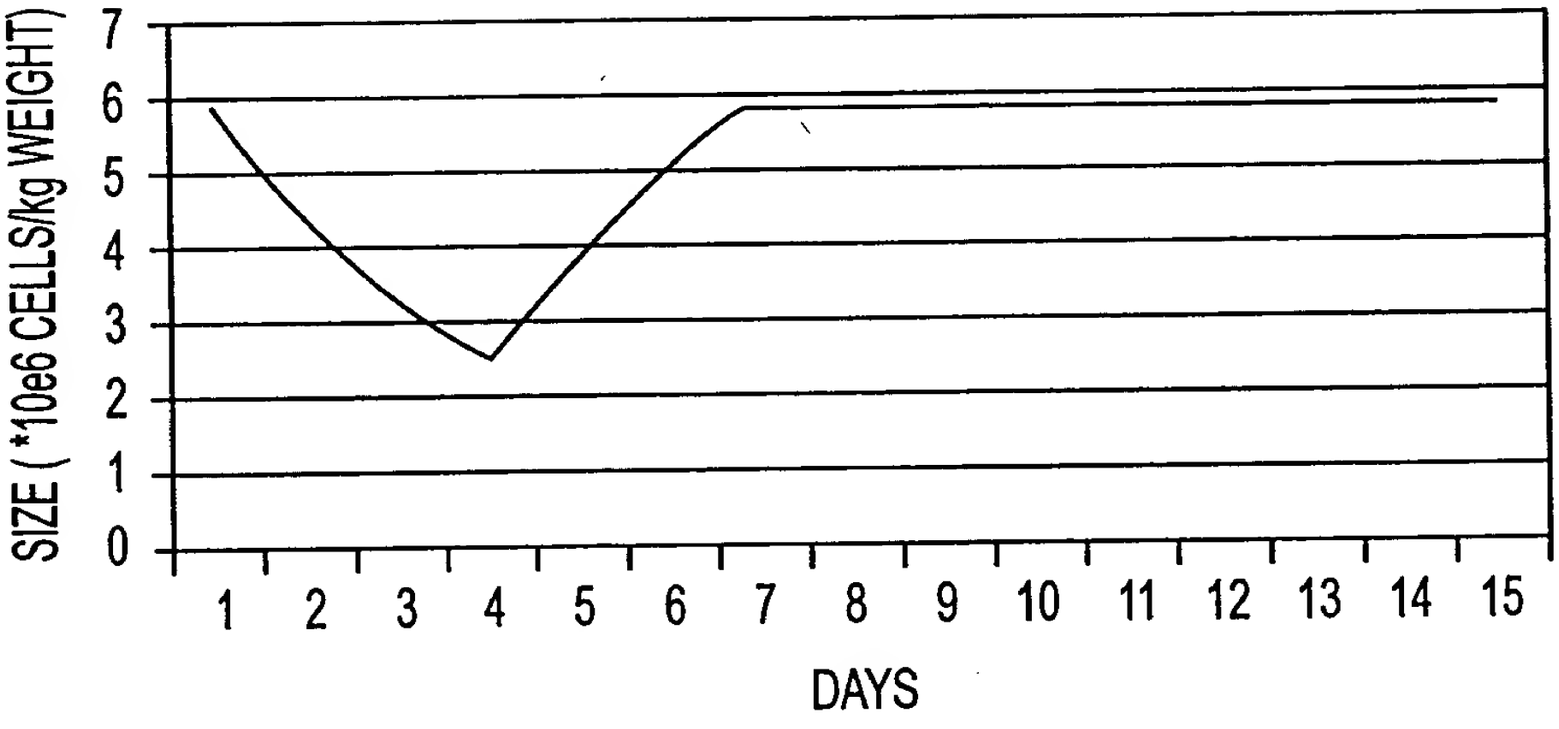
SIZE (*10e6 CELLS/kg WEIGHT)
0
1
2
3
4
5
6
7
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
DAYS

FIG. 11

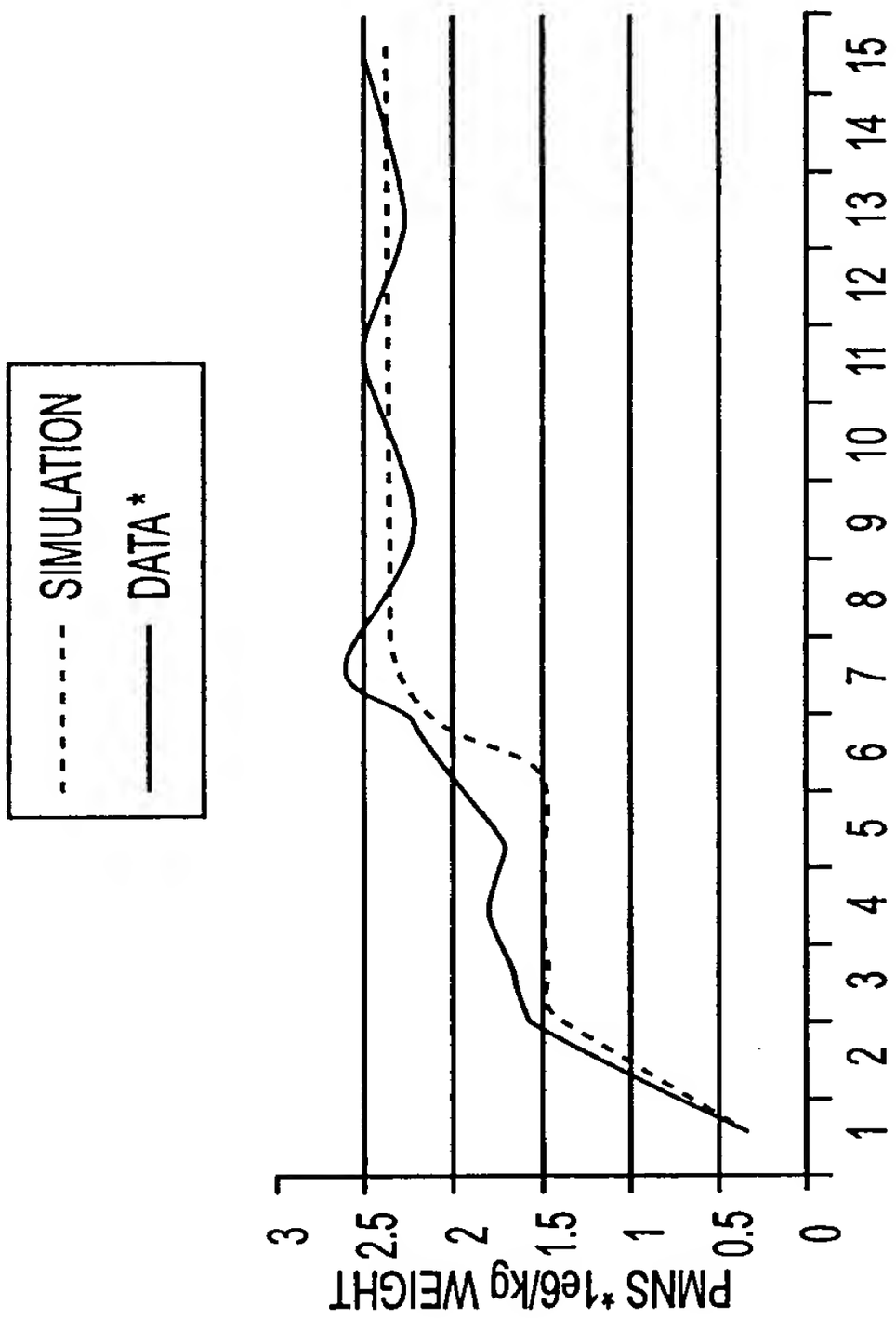

FIG. 12B

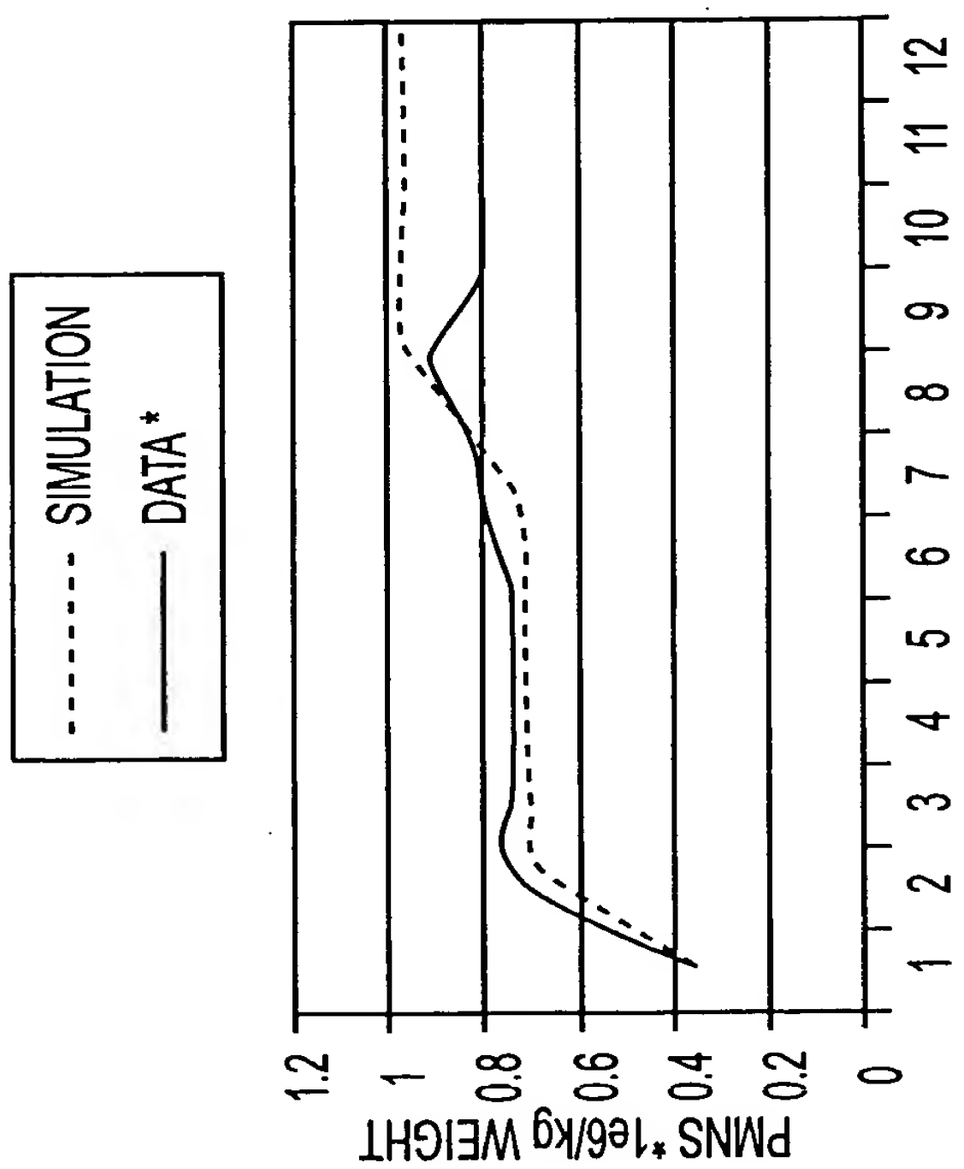

FIG. 12A

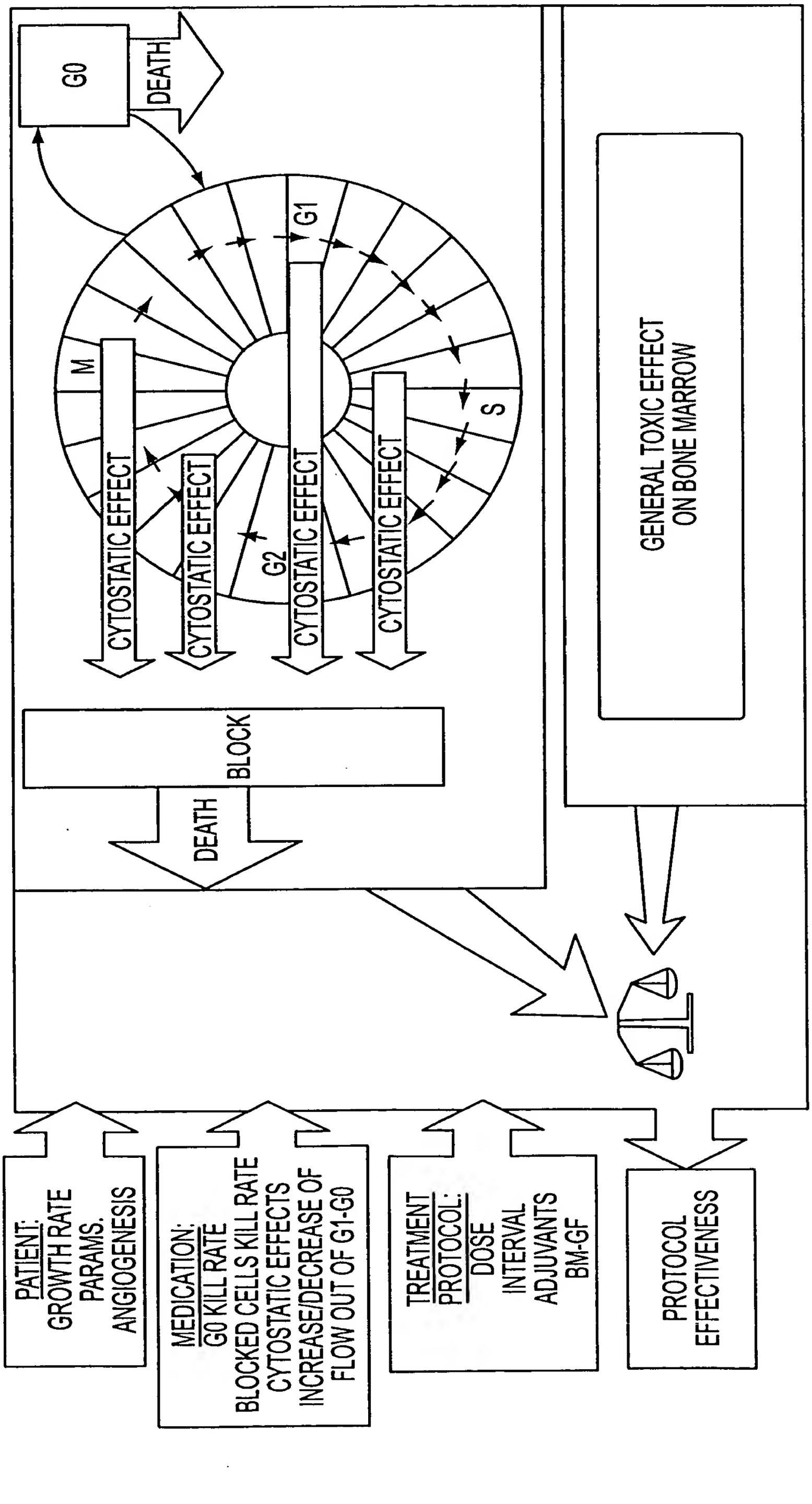
G0
DEATH
G1
S
G2
M
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
BLOCK
DEATH
GENERAL TOXIC EFFECT
ON BONE MARROW
PATIENT:
GROWTH RATE
PARAMS.
ANGIOGENESIS
MEDICATION:
G0 KILL RATE
BLOCKED CELLS KILL RATE
CYTOSTATIC EFFECTS
INCREASE/DECREASE OF
FLOW OUT OF G1-G0
TREATMENT
PROTOCOL:
DOSE
INTERVAL
ADJUVANTS
BM-GF
PROTOCOL
EFFECTIVENESS

FIG. 13

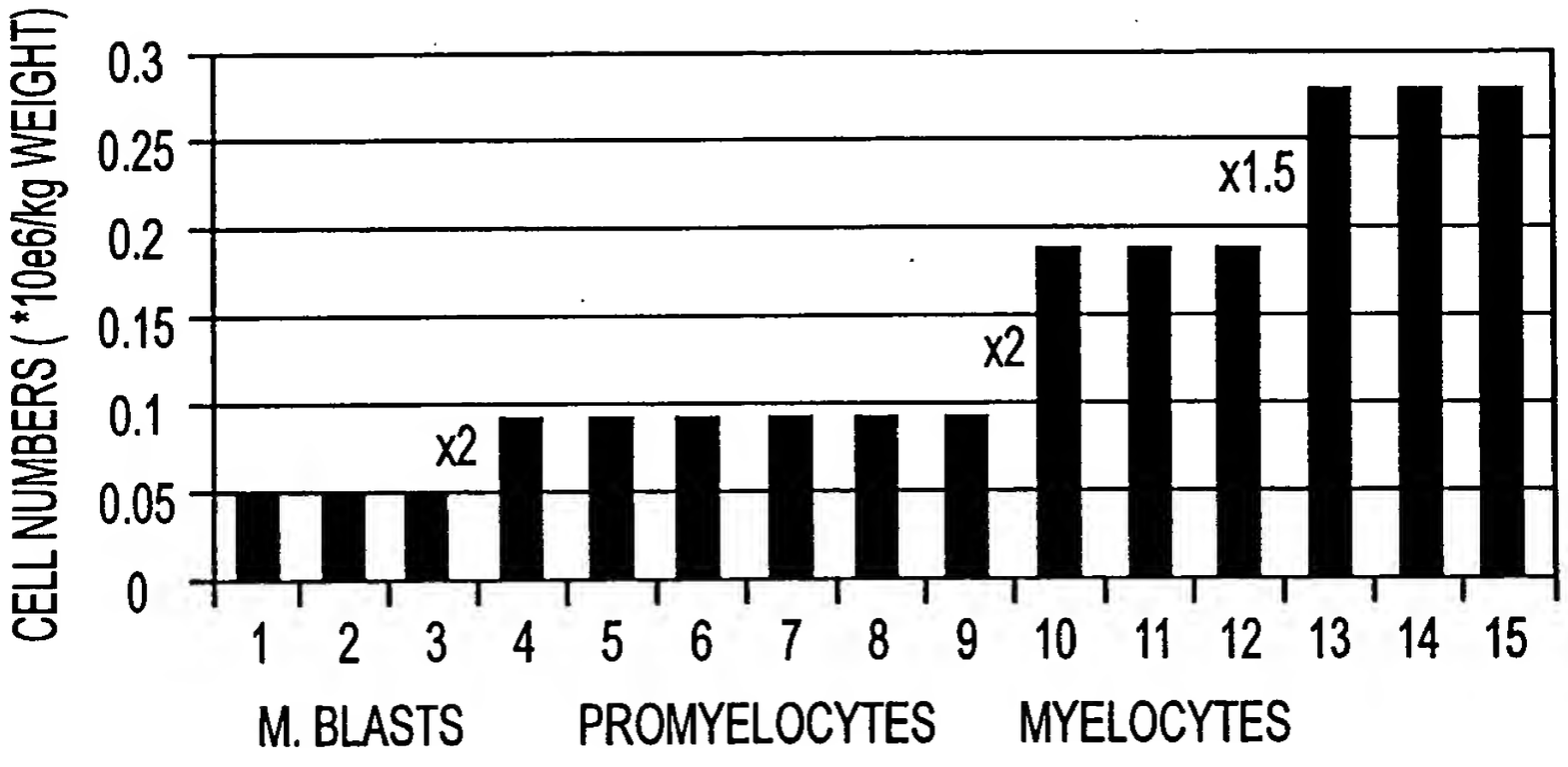
CELL NUMBERS (*10e6/kg WEIGHT)
0.3
0.25
0.2
0.15
0.1
0.05
0
x2
x2
x1.5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
M. BLASTS
PROMYELOCYTES
MYELOCYTES

FIG. 14

16/16

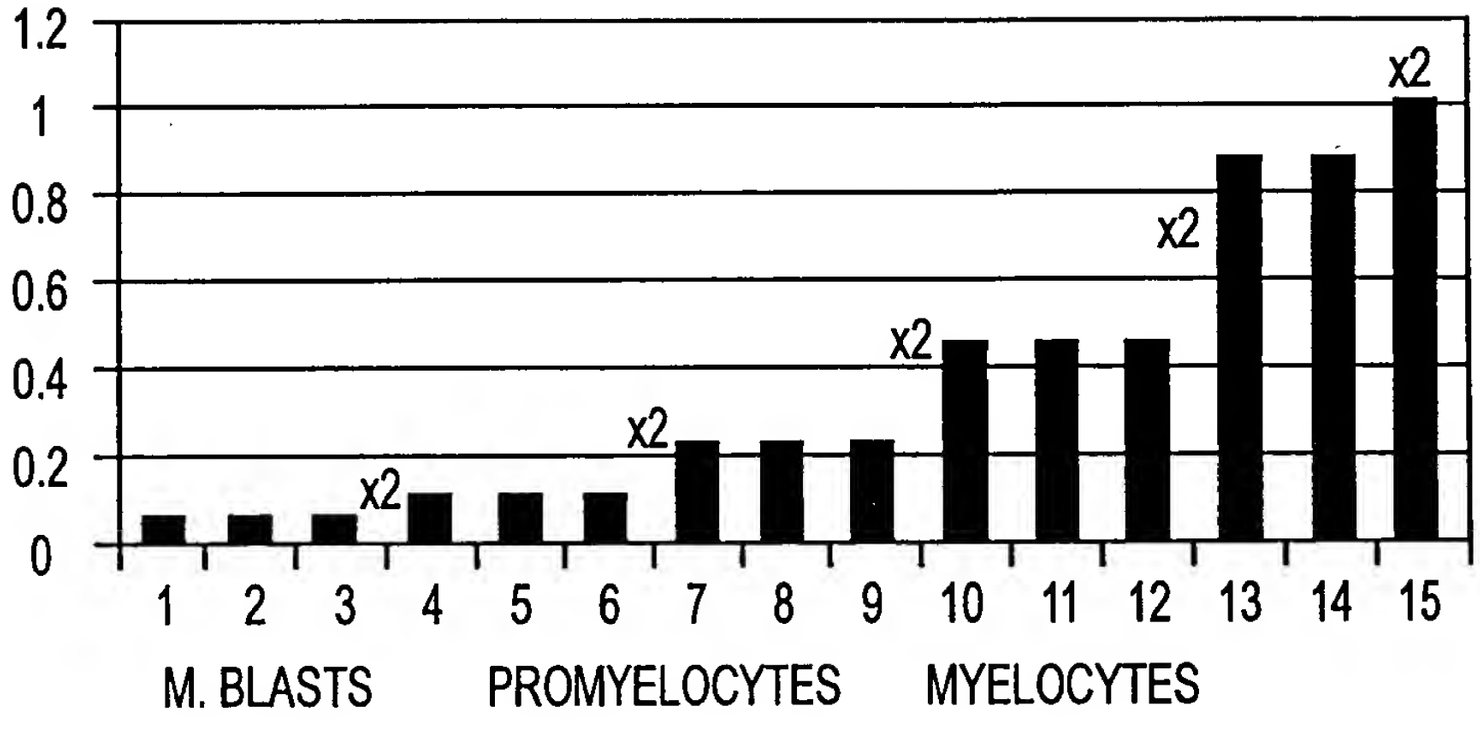
1.2
1
0.8
0.6
0.4
0.2
0
x2
x2
x2
x2
x2
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
M. BLASTS
PROMYELOCYTES
MYELOCYTES

FIG. 15